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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
HABTE, KAHSAY

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 09/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/058,215	Applicant(s) LU ET AL.	
	Examiner Kahsay Habte, Ph. D.	Art Unit 1624	

-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-65* is/are pending in the application.

4a) Of the above claim(s) *51-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-37,40-50 and 54-65* is/are rejected.

7)☒ Claim(s) *38 and 39* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4-7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-65 are pending.

Election/Restriction

2. Applicant's election with traverse of Group V, Claims 1-50 and 54-65 in Paper No. 11 is acknowledged. The traversal is on the ground(s) that the claims of Groups V, VI and VII fall into the same class (class 546). This is not found persuasive because while the claims are classified in the same class they fall within different subclasses and thus require different searches. For example for Group VI additional search is required in subclasses 546/118 and subclasses 546/126. For Group VIII, additional search is required in subclass 546/277.4. Thus, coexamination of each of the additional groups would require search of subclasses unnecessary for the examination of the elected claims. Therefore, coexamination of each of these additional inventions would require a serious additional burden of search.

Note that Group V (naphthyridines) is classified in subclass 546/122.

The requirement is still deemed proper and is therefore made FINAL.

3. The claims are drawn to multiple inventions for reasons set forth in the restriction requirement. The claims are examined only to the extent that they read on the elected invention. Cancellation of the non-elected subject matter is recommended in response to this Office Action.

Cl im Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 41-42, 44-45 and 63 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for many of the diseases recited in claim 54, does not reasonably provide enablement for the treatment of tumor growth, metastasis, restenosis or inflammation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. There has been recited a method of treating tumor growth, metastasis, restenosis or inflammation

The claim sets forth the treating a pathological condition selected from the group consisting of tumor growth. However, there never has been a compound capable of treating tumor growth including metastasis generally. There are compounds that treat a range of cancers, but no one has ever been able to figure out how to get a compound to be effective against tumors generally, or even a majority of tumors. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety

of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancer growth generally, evidence that the level of skill in this art is low relative to the difficulty of such a task.

Further, "tumor" covers more than just cancers. It also covers many neoplasms, cancerous or not. A neoplasm is any abnormal tissue that grows by cellular proliferation more rapidly than normal, or continues to grow after the stimulus that initiated the new growth has ceased, or shows lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such a term, also covers precancerous conditions such as lumps, lesions, and polyps. In addition, "tumor" covers things other than neoplasms. It also covers any kind of swelling arising from inflammation. Thus, the claim would cover treatment of many kinds of inflammation. The specification cannot support that.

When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, *In re Ferens*, 163 USPQ 609. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs Novo Nordisk*, 42 USPQ2nd 1001, 1006.

In claim 41 and 44, there has been recited a method of treating restenosis, but the specification is not enabled for such a scope. Restenosis, or recurrent stenosis, is an extremely general term. Stenosis is the narrowing of any canal, orifice, valve, duct, artery, vein, tube (such as trachea), opening, etc. in the body. These can arise from obstructive lesions, deposits of granulations, organ hypertrophy, etc. There is no such thing as being able to treat such widely diverse problems which arise from different sources.

Enablement for the scope of "inflammation" generally is not present. For a compound or genus to be effective against inflammation generally is contrary to medical science. Inflammation is a process which can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, assorted leukotrienes and cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally.

Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and

recruitment of circulating neutrophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages which have stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters.

Otitis media is an inflammation of the lining of the middle ear and is commonly caused by Streptococcus pneumoniae and Haemophilus influenzae. Cystitis is an inflammation of the bladder, usually caused by bacteria. Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics.

Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications (Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases. The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms and treatment (or lack thereof) for

inflammation. It establishes that it is not reasonable to any agent to be able to treat inflammation generally.

5. Claims 54-55, 60 and 64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for most of the diseases recited in claim 54, does not reasonably provide enablement for the treatment of neuronal loss associated with stroke, neurodegenerative disease and an adverse consequence of overstimulation of one or more excitatory amino acids. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. There has been recited a method of treating neuronal loss associated with stroke, neurodegenerative disorder and an adverse consequence of overstimulation of one or more excitatory amino acids, but the specification is not enabled for such a scope.

Stroke represents one of the most intractable medical challenges. Stroke is estimated to cause about 15% of deaths, behind only heart disease and cancer. Even those who survive normally suffer from persistent damage, including motor and speech disturbances and/or convulsions. Despite a tremendous effort to resolve these problems, cerebrovascular therapy as so far been limited to trying to prevent further damage in areas on the margins of the ischemic focus, thus trying to maintain adequate perfusion in remaining intact areas, and thereby limit progressive infarction. This is generally done surgically. Standard pharmaceutical treatment, such as antiarrhythmics

and antithrombotics don't get at the cause of the stroke or the damage caused, but are mostly done to insure adequate cardiac functioning.

Effective acute drug treatment of the stroke itself has so far proved to be beyond the reach of medical science. Major efforts have certainly been pressed in the area of neuroprotective therapeutics. Those studied have included use of Ca antagonists such as Levemopamil and flunarizine, to suppress neuronal calcium influx; NMDA antagonists (both competitive, such as APV and CPP, and non-competitive such as chlorpromazine, ifenprodil and Mg salts) as well as AMPA and kainate antagonists to block post-ischemic receptor-operated calcium channels; attempts to block arachidonic acid cascade or elimination of its metabolic products with agents such as lipogenase inhibitors and thromboxane; use of free oxygen radical scavengers such as superoxide dismutase, alpha-tocopherol, or allopurinol to inhibit the lipid peroxidation that damages cell membranes, which may indirectly help prevent intracellular calcium overload; anti-edema agents such as corticosteroids; use of 5-HT_{1A} receptor agonists to suppress 5-HT concentrations in the hippocampal extracellular space; use of CRF receptor antagonists to inhibit excitotoxic brain damage; use of serotonin 1A agonists such as ipsapirone, or adenosine modulators such as vinpocetine, to stimulate adenosine, which may act as a protective agent by hyperpolarizing the postsynaptic neuron; use of platelet aggregation inhibitors such as prostacycline and ticlopidine, and other approaches as well.

Despite this vast outpouring of research, the skill level in this art is sufficiently low relative to the difficulty of the task that obtaining a neuroprotective treatment of stroke

was, as of the filing date, not yet possible. Hence, accomplishing such a goal involves more than routine experimentation. As evidence for this, there is cited Chalmers (TiPS Vol 17, pages 166-172 April 1996), which states flatly on page 170 that, "At present, there are no effective neuroprotective agents that can clinically ameliorate the effects of stroke in humans." For example, Pentoxifylline has been one of the most intensely studied, with dozens of studies published on its properties. It appears to have a wide variety of effects on leucocytes, erythrocytes, neutrophils, plasma fibrinogen levels. These result in a wide-ranging ability to increase blood flow, resulting in effectiveness in some vascular disorders, especially intermittent claudication. Research with different administration methods, or different subcategories of stroke may well result in the discovery of how to get this drug to work, but the slowness and difficulty of this research shows clearly that this involves undue, not routine experimentation. Applicants' compounds have been subjected to far less study.

There is no such an agent, which can treat neurodegenerative disorders generally. That is because neurodegenerative disorders are extremely varied in origin and nature of effect. The origin and the nature of many neurodegenerative disorders such as Huntington's disease, Pick's disease, Frontotemporal dementia, Cerebro-Oculo-Facio-Skeletal (COFS) syndrome (cranofacial and skeletal abnormalities), Motor neuron disease (muscle weakness), Corticobasal ganglionic degeneration, Creutzfeldt-Jacob disease (fatal disease), Dementia with Lewy bodies, and Progressive supranuclear palsy Dementia are different one from the other. Many neurodegenerative disorders are

untreatable to this day. For example, autism and mental retardation are some of the neurological disorders that have no pharmacological treatment.

The symptoms and nature of these diseases are also different one from the other. It can be shown that many of these neurodegenerative disorders have different origin and nature of effect. Some neurodegenerative disorders are hereditary (Charcot-Marie-Tooth disease). Many neurodegenerative disorders vary in how they affect the body and its functions. Diseases such as Cerebral palsy, and Parkinson's disease affect the movement of the patient. Diseases such as Alzheimer's disease affect the memory of the patient. Because the nature of neurodegenerative disorders extremely vary one from the other and the fact that autism and mental retardation are untreatable to this day, it is appropriate for the examiner to raise an enablement rejection.

There has been recited in claim 54 for treating an adverse consequences of overstimulation of one or more excitatory amino acids (EAA) in general, but the specification is not enabled for such a scope. Applicants are claiming the treatment of all adverse consequences of overstimulation of one or more excitatory amino acids, but to this day no one was able to treat all adverse consequences of overstimulation of one or more excitatory amino acids. According to a recent review article by Alfred Meijer {The Journal of Nutrition; Jun 2003; 133, pages 2057S-2062S}, "Amino acids are not only important precursors for the synthesis of proteins and other N-containing compounds, but also participate in the regulation of major metabolic pathways." There are about 20 amino acids commonly found in proteins. On page 2057 (first column, last

paragraph), the reference discloses examples of amino acids as regulators of metabolism. For example, alanine controls the inhibition of L-type pyruvate kinases that are considered to be in relevance in fasting. Role of glutamate and asparate in mediating the transfer of reducing equivalents across the mitochondrial membrane via the malate/asparte shuttle, e.g. during aerobic glycosis, in heart, skeletal muscle and brain, and during ethanol oxidation in the liver. Applicants are directed to refer to pages 2057-2058 that show different examples for the role of amino acids in metabolism. This article clearly shows that the role of amino acids in the body is very diverse. Thus, applicants claim of treating any adverse conditions that arise from overstimulation of amino acid/amino acids is not enabled.

Glutamate is the main excitatory neurotransmitter in the body. It is essential for learning, and for both short-term and long-term memory. It is also the precursor to the inhibitory neurotransmitter, GABA. GABA is a calming neurotransmitter, and is essential for speech. Other excitatory amino acids include, aspartate, cysteine, homocysteine and possibly more. Excess levels of glutamate have been possibly implicated in a range of neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, Huntington's chorea, stroke, Multiple sclerosis, and ALS. In the case of autism, irregularities related to glutamate have been observed. In addition, glutamate, glutamic acid and aspartate and aspartic acid were found to be elevated in individuals exhibiting autistic behavior relative to controls.

The amino acid L-Glutamate is a neurotransmitter in many central excitatory pathways. In addition, certain other naturally-occuring amino acids, such as L-Aspartate

and L-Homocysteate also have excitatory actions. All of these exert their actions via a number of receptors. The classification and identification of these receptors has been the subject of intense study by many workers over several decades. An outline of this work is presented below.

Glutamate is a well-studied excitatory amino acid. Excess amount of glutamate is implicated in diseases such as neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, Huntington's chorea, stroke, Multiple sclerosis, and ALS. In addition, glutamic acid and aspartate and aspartic acid were found to be elevated in individuals exhibiting autistic behavior relative to controls. Note that Alzheimer's disease, Parkinson's disease, stroke, Multiple sclerosis, and ALS are hard to treat disease, whether they are linked with EAA or not.

Very little is known about the adverse consequences of the other three excitatory amino acids (aspartate, cysteine, or homocysteine). There might be still other excitatory amino acids that are even less well understood. Since applicants are claiming the treatment of <u>any</u> adverse consequences of one or more excitatory amino acids that covers the 4 known ones and other unknown excitatory amino acids, enablement for such a scope is not possible since so little or nothing is known about what these consequences are.

Even if applicants were to be entitled to glutamate, the treatment would not be enabled since glutamate is linked to diseases that are hard to treat to this day. It is up to applicants to provide scientific evidence that shows the treatment of all adverse consequences of overstimulation of EAA.

6. Claims 54, 61 and 64 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. There has been recited a method of treating neurodegenerative disorder selected from Alzheimer's disease or Parkinson's disease, but the specification is not enabled for such a scope.

The central characteristic of Alzheimer's disease is the deficiency in the level of the neurotransmitter Acetylcholine that plays an important role in memory. Alzheimer's disease can be treated only by Acetylcholinesterase inhibitors that reduce the depletion of acetylcholine. The skill level in the art is so low that the only treatments available to this day are drugs that inhibit Acetylcholinesterase.

Parkinson's disease is a neurological disorder that is also characterized by rhythmic muscle tremors, hypokinesia, and muscular rigidity. Dopamine, a hormonelike substance is an important neurotransmitter in both the central and peripheral nervous systems that is currently used as treatment for Parkinsonism. Dopamine is a neurotransmitter involved in the regulation of the central nervous system. The skill level in the art is such low that the only treatments available to this day are drugs that are helpful in regulating Dopamine. Thus, a rejection under 35 U.S.C. 112, first paragraph is proper.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

Claims 1-50 and 54-65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention:

a. Claim 1 and claims dependent thereon are rejected because the phrase "such as" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

b. In claim 54, the method for treating "surgery" is not clear. "Surgery" is a medical procedure but not a disorder.

c. In claim 54, the method for treating "anesthesia" is not clear. "Anesthesia" is a state deliberately induced by the administration of anesthetics. It is not a disorder.

d. In claim 54, the phrase "an adverse consequence of overstimulation of one or more excitatory amino acids" is not clear. Scope is unknown. What are all the consequences? Which amino acids are covered and which are not? Which amino acid is linked to what adverse consequence?

Objection

8. Claims 38-39 are objected to as being dependent upon a rejected base claim and also contain species from non-elected inventions, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims and cancellation of the species of non-elected inventions.

Conclusion

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kahsay Habte, Ph. D. whose telephone number is (703) 308-4717. The examiner can normally be reached on M-F (9.00AM- 5:30PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on 703-308-4716. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Kahsay Habte, Ph. D.
Examiner
Art Unit 1624

Mukund J. Shah
Supervisory Patent Examiner
Art Unit 1624

KH
September 2, 2003